Aus dem Laboratorium für Klinische Chemie und Lipidforschung
(Leiterin: Prof. Dr. I. Kupke)
der Kinderklinik A der Universität Düsseldorf
(Direktor: Prof. Dr. G.-A. von Harnack)

EARLY INDICATORS FOR THE RISK OF ATHEROGENESIS. A FIELD TEST OF A NEW METHODOLOGY ON KINDERGARTEN CHILDREN IN DUESSELDORF

Dissertation

zur Erlangung des Grades eines Doktors der Medizin
der Medizinischen Fakultät der Universität Düsseldorf

vorgelegt von

Barbara Heller und Peter Weiss

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EARLY INDICATORS FOR THE RISK OF ATHEROGENESIS. A FIELD TEST OF A NEW METHODOLOGY ON KINDERGARTEN CHILDREN IN DUESSELDORF

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S U M M A R Y

566 children (3-7 yr) in 17 kindergartens have been examined with regard to height, weight, blood pressure and various constituents of capillary blood serum: glucose (GLUC), uric acid (UA), total cholesterol (TC), free cholesterol (C), cholesterolesters (CE), triacylglycerols (TG), phosphatidylethanolamine (PE), phosphatidylcholine (PC); α-, pre-β- and β-lipoprotein cholesterol (α-LP, pre-β-LP, β-LP). Micromethods recently developed in this laboratory provide analyses of the lipids and lipoproteins (LPs) in a total of only 31 µl capillary blood serum. Several sub-groups were discerned among the children tested: Children in 12 kindergartens were regarded as representing an average pediatric population; children in 5 other kindergartens belonged to a socially underprivileged group. Among the children in the average group, 335 were anthropometrically within the normal limits; this group was regarded as a reference sample group and their blood served for the evaluation of reference values. The concentrations used in defining the reference values were normally distributed and were largely consistent with published data on children of similar age in several Cental European and American cities. In addition, 8 sub-groups of the reference sample group with members lying in the tails of the concen - tration distributions were considered separately.

Another group (n=22) was overweight. Among the 117 socially underprivileged children, 96 were also anthropometrically within the normal limits but 14 children showed retarded growth. Blood pressure was nearly the same in all groups.

In overweight children the content of TC was significantly reduced at the expense of β-LP. The other parameters did not differ from the reference sample group, nor did the correlations between the metabolic pairs tested.

The socially underprivileged children with anthropometric data within the normal range showed a reduction of several blood constituents: GLUC, PC, TC, pre-β-LP and α-LP; the PC:PE ratio was diminished.

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The correlations between the metabolic pairs tested did not differ from those of the reference sample group - with the exception of TG:α-LP, which showed an inverse relation. The latter result also applies to hypo-α-lipoproteinemia and hypercholesterolemia. Children with retarded growth had lost the coordination of CE:C - in common with hypercholesterolemic children. Although their concentrations were diminished, there were positive correlations of PC: α-LP and GLUC: α-LP, but an inverse relation of GLUC:TG and TG: α-LP.

This study represents a field test of a new methodology and confirms its suitability for the examination of young children outside the clinic. Ten constituents of capillary blood serum were evaluated. The results show clearly that significant metabolic alterations can be detected in apparently healthy children, and the same is true for overweight and socially underprivileged children. Many of the same alterations can be observed in adult atherosclerosis. During the last decade, the World Health Organization and other groups have made appeals for the examination of young children with regard to atherogenesis. Our results confirm that this is a highly desirable goal and our methodology appears both adequate and appropriate for this task.

Key words: Kindergarten children - Atherosclerosis - Risk indicators - Reference sample group - Subgroups - Overweight - Socially underprivileged children - Reference values - Glucose - Uric acid - Lipid profiles - Lipoproteins - New micromethods - Field test

I N T R O D U C T I O N

Atherogenesis is known to progress for many decades before its clinical manifestation (1-6). Accordingly, metabolic alterations in the arterial tissues related to the disease will necessarily occur prior to the development of arterial lesions and clinical symptoms. In animal experiments, metabolic disorders typical of atherosclerosis have been found in aortas and coronary arteries under various experimental conditions; however, these metabolic alterations are not associated with any morphological changes detectable by light-microscopy (7-10). Possibly, these metabolic disorders represent an early stage of atherogenesis which might be the beginning of the "silent phase" of the disease (4,5,11). However, as much as the study of animal models may aid in understanding the etiology of the disease and in developing methods for its management, early indicators specific for the risk in humans need to be identified. Since the rate of regression may be related to the length of the induction period (12,13), the search for these risk indicators should begin at as early an age as possible. Accordingly, prevention of atherosclerosis has been recognized during the last decade to be in large part a pediatric problem (14-22). There is no doubt that there is a need for prevention in childhood (23).

As the blood lipids and lipoproteins (LPs) have been found to play a key role in atherosclerosis, assay of these metabolites is certainly meaningful (24-28). Studies on adult subjects have shown that it is more informative to measure several lipids rather than only one (29). Moreover, the distribution of these lipids, particularly of total cholesterol (TC), among the LP fractions has proved to be a valuable tool for diagnosing disorders in lipid metabolism (28,30-32). Procedures suitable to this purpose ought to be simple and precise, yet inexpensive and applicable to the examination of large population samples including very young children (11,22).

In order to meet these requirements, we have developed micro- and ultramicromethods which have proved to be adequate for this purpose: A total of 31 µl capillary blood serum is sufficient for analyzing various serum lipids together with the cholesterol in LP fractions (33-3

Using these new procedures, we have examined 566 children in 17 kindergartens in Duesseldorf. The children were in the fasting state; height, weight and blood pressure were measured and capillary blood obtained. The serum was analyzed for several metabolites: glucose (GLUC), uric acid (UA); serum lipids such as total cholesterol (TC), free cholesterol (C), cholesterolesters (CE), triacylglycerols (TG), phosphatidylcholine (PC) and phosphatidylethanolamine (PE); β-lipoprotein cholesterol (β-LP), pre-β- lipoprotein cholesterol (pre-β-LP) and α-lipoprotein cholesterol (α-LP).

The aim of this study was to provide a field test of a new methodology applicable in preventive medicine, in particular in pediatrics. Reference values of variables related to the risk of atherogenesis were established. The results on children with extreme concentrations of several serum constituents shed light on an extreme metabolic state of apparently healthy children. The influence of overweight and negative socio-economic living conditions was also studied. Criteria already accepted as indicating a risk of atherogenesis in adults were applied to these young children and are discussed in terms of "eraly indicators" of the disease. Excerpts from this work were previously reported (39, 40).

S U B J E C T S A N D M E T H O D S

S u b j e c t s

From November 1977 to February 1978, 566 children (3-7 yr) in 17 kindergartens in Duesseldorf were examined. Provided permission was given by the head nurse of each kindergarten, written information on the content and goals of the examination was given to the nurses, parents or guardians at least one week beforehand. It was clearly pointed out that the examination would be performed on a voluntary basis and that only

children whose parents or guardians had given written consent would be examined. About 95 % of the parents and guardians were extremely interested in the topic and asked to be examined, too, as did of many of the nurses. The results were made available to the parents or guardians via the head nurses. In some cases, parents were advised to consult their pediatrician.

The children were in the fasting state and remained seated during the examination. Blood pressure, height and weight were measured. For blood sampling, hyperemization of one finger tip was induced by applying an analgesic cream for 10 min. (infraRUB, Whitehall Lab. Inc., New York, NY 10017, U.S.A.) followed by another 10-15 min. of bathing the entire hand in warm water. Blood was obtained by lancing the finger tip; the first drops of blood were discarded; squeezing of the finger tip was strictly avoided. 500-1000 µl capillary blood could easily be collected from each child. Serum was obtained after clotting by centrifugation within 2 hours and analyzed within 2 days.

It should be mentioned that we made an effort to take the special situation of children as subjects in our investigations into account: All children were allowed to watch the examination and the taking of blood samples. Questions were answered in a way they could understand. Only a few children were anxious; these had the chance to paint or play before donating the blood, or to refuse to participate. The children's attention was directed to a large number of small transparent containers filled with colored fruit gum either all of one color or mixed in various combinations. As a reward, one container was given to the child at the end of the examination. The choice of the favorite color was a successful and amusing distraction. As another reward, fresh peaches were served to the children. In further studies on Japanese children, bathing the hands in warm water was done with colored foam rubber sponges; squeezing these sponges not only promoted hyperemization but also created a relaxed atmosphere. If wanted, the child received a piece of glucose-based chocolate on his tongue directly before the finger tip was lanced (in preparation).

Among the 566 children investigated, 69 were from the Mediterranian countries and Japan. Data obtained on these children are not included in this report. The remaining 497 German children were differentiated as follows. According to socioeconomic criteria, 2 groups were discerned: Children from 12 kindergartens were regarded as an average population representative of an industrial city such as Duesseldorf, while children of 5 kindergartens belonged to a district classified by the local authorities as socially underprivileged. These 2 groups were further sub-divided according to anthropometric criteria (41). Among the average pediatric population (n=380), children whose age-related height was below the 3rd percentile (n=5) and above the 97th percentile (n=16) were excluded from the study. Twenty-two children were overweight (more than 15 % above the normal height-related weight). The remaining 335 children had normal age-related height and weight and were designated as the reference sample group. The blood of this group served for the evaluation of reference values; children whose values ranged beyond the normal limitswere considered separately. Among the 117 socially underprivileged children, 96 were anthropometrically "normal"; however, 14 of these children had retarded growth and were examined separately.

Methods

Determination of glucose and uric acid

GLUC and UA were determined enzymatically using test combinations (GLUC: hexokinase reaction; Boehringer, Mannheim, F.R.G.).

Phenotyping of lipoprotein patterns

A micro-electrophoresis system was used (Corning-EEL/IMA, Gießen, F.R.G.).

Determination of lipids

The lipid profiles (CE, C, TG, PC, PE) were analyzed by high-performance thin-layer chromatography (HPTLC) (33). After direct application of 0.5 µl serum to the silica-gel layer, the lipids were separated and quantitated by fluorescence measurement. Standardization of this

method revealed that the coefficients of variation were ≤ 2.8 % for all lipids tested, and recovery of known amounts of lipid 96-100 %. There was a close correlation between data obtained by reference methods and HPTLC.

For comparison of data, several lipids of the children were analyzed enzymatically using Test-Combinations (TC and C: katalase method, TG: fully enzymatic method; Boehringer,Mannheim, F.R.G.).

Determination of lipoprotein cholesterol

A new micro-procedure for the determination of lipoprotein cholesterol (LP-TC)was used (34-36): The LP fractions of 15 µl serum were separated on the same day by electrophoresis on agarose gel. The samples were dried, dissolved in HCl, and neutralized with a saturated Tris solution producing a Tris-buffer system at pH 7. This system was found to be highly suitable for enzymatic determination of LP-TCin the presence of agarose. The kinetic properties and linear range of this reaction system, the precision (coefficient of variation 1-3 % and recovery of TC (100 %)) were found to be optimal. This microprocedure gave nearly identical results to those obtained with ultracentrifugation (37).

Analytical control

Analyses of GLUC, UA, TC and TG were subject to internal and external quality control. TC, C and TG were determined by 2 methods - enzymatically and by HPTLC. For quantitative LP electrophoresis, recovery of LP-TC ≥ 95% was strictly required in each case. In 1979/80, we had the opportunity to verify the standardization for TC, TG and α-LP analyses using our new microprocedures. Reference samples kindly supplied by the Center of Disease Control, Public Health Service, Atlanta, Georgia, U.S.A. were analyzed with these procedures; the results ranged within the limits of the CDC-survey.

Statistical methods

The type of distribution of data was evaluated by the Kolmogorov-Smirnov goodness-of-fit test; pairs of variables were examined by linear regression analysis; groups were compared by a non-parametric test according to Mann-Whitney.

RESULTS AND DISCUSSION

This study provides a field test of a new methodology applicable in preventive medicine, in particular in pediatrics. Since taking capillary blood is less dangerous than venepuncture, our analytical procedures, which permit measurement of 8 constituents in only 31 µl capillary blood serum, certainly meet the requirements of large-scale studies outside the clinic, and also provide an especial advantage in the examination of young children.

As regards the new procedures for lipid and LP analysis, these yielded results nearly identical to those obtained using the current reference methods (Tab. 1). Furthermore, analysis of reference matarials kindly supplied by CDC/Atlanta gave data which ranged within the limits of the CDC-survey. This gave us further confirmation of the reliability of our new procedures, as well as their suitability for epidemiological studies.

Anthropometric criteria and blood pressure

In order to avoid interference with ethnic factors, only data obtained on German children are presented in this report. Tab. 2 include data on age, height, weight and blood pressure. Although not measured under standardized conditions, the blood pressure of the reference group was nearly identical with the standards reported for American children of the same age (42). Among the 117 socially underprivileged children, 96 (82 %) were anthropometrically normal and also had normal blood pressure. The remaining 14 children were of the same age (5 $\pm$ 2 yr) as the rest but showed retarded growth (height = 98 $\pm$ 10 cm, weight = 14.6$\pm$2.2 kg), known to occur for example in malnutrition syndromes (43). The blood pressure of these children seemed to be slightly lower than in the reference sample group (86$\pm$13 / 50$\pm$9 mm Hg). Another group (n=22) of the same age had overweight; however, the other parameters were nearly the same as in the reference sample group. These data suggest that in 82 % of the socially underprivileged

children, negative socioeconomic living conditions did not influence age-related height and weight. Blood pressure was not unequivocally influenced, either by negative living conditions or by overweight, at least at this early age.

R e f e r e n c e s a m p l e g r o u p

The 335 children in the average pediatric population ranged within the normal limits of anthropometric criteria and normal blood pressure (Tab. 2). The serum constituents measured in the capillary blood serum of these children provide reference values, produced and presented according to the Provisional Recommendation on the Theory of Reference Values (44). In addition, members of this group lying in the tails of the concentration distributions represent metabolic patterns which will be discussed separately below as "sub-groups".

Reference values

Tab. 3 presents reference values of various blood constitutents discussed as being directly or inversely related to the risk of coronary artery disease. All data were normally distributed (Fig. 1a - d). The data found for the percent distribution of TC among the LPs were also normally distributed. Disregarding the details of the methods used in each case, we have compared our data obtained on children in Duesseldorf with those reported for other pediatric populations in several other Central European and American cities (32,45-53). As may be seen from Tab.4, the lipid and LP levels of our children are comparable to those of several other groups. Interestingly, children from Citadella (North Italy) (47) and the Eastern United States had nearly the same levels of TG but lower levels of TC.

Furthermore, ratios of various metabolic pairs were calculated and several variables examined by linear regression analysis (Tab.5 and 6). Among 26 pairs tested, only 7 showed a relatively close positive correlation: TC:C, TC:CE, and CE:C, partly related to each other by the lecithin:cholesterol acyl-transferase reaction (54); TC:β-LP, known to

be positively correlated in adults (24). Furthermore, the correlation of TC: α-LP within our group was weak but significant ($r=0.38$, $P<0.0$

Interestingly, a positive correlation was observed for the concentrations of TC and high-density lipoproteins (HDL) evaluated with different methods in different countries: TC:HDL = 2.6-3.3, $y=0.20x + 0.52$, $r=0.5$ $P<0.05$ (Tab.5). This result is largely consistent with data from an international study on young boys whose serum-TC and HDL were analyzed in the same laboratory: intra-group correlation was relatively weak ($r = 0.2-0.5$), but inter-group correlation was close and highly significant ($r = 0.90$, $P<0.001$) (46).

As shown in Tab. 3, PC comprised one third of the total serum lipids 50 % of the PC being associated with HDL (55). Correlation analysis of PC:PE revealed a moderate yet significant association (Tab. 5), thus reflecting a coupled metabolic control dependent on transmethylation processes(56,57). Moreover, there was a weak but significant correlation between serum-PC and α-LP (Tab. 5). It is tempting to speculate that several phenomena observed in regression studies (58,59) might be related to this inherent factor.

S u b - g r o u p s

Hyperglycemia

As shown in Tab. 7a, 10 children exhibited moderate hyperglycemia associated with relatively low levels of TC, β- and α-LP but with levels of pre-β-LP within the upper normal range, the β:α-LP ratio in 6 of the 10 children varied within the lower limits of normal. This metabolic pattern was pronounced in one child (No.5) who had the highest GLUC concentration. Furthermore, the GLUC levels of this group were negatively correlated with TC and β-LP but showed a positive correlation with pre-β-LP (Tab.6). Similar results have been reported for carbohydrate-induced alterations of very-low density lipoproteins (VLDL), Type IV hyperlipoproteinemia, obesity, and diabetes mellitus (34, 60-64). Moreover, there was a tendency for

serum-TG and α-LP to be inversely correlated. The latter result was also true for the groups exhibiting hypercholesterolemia, hypo-α-lipoproteinemia, and for socially underprivileged children (Tab.6). Although the levels of serum-TG and α-LP were not altered unequivocally in this hyperglycemic group (Tab. 7a), their reciprocal relationship might hint at an ineffective lipoprotein lipase activity known to be directly related to the risk of CHD (65). Whether or not these metabolic patterns indicate a transient diet-induced metabolic state or some type of diabetes mellitus remains to be elucidated.

Hyperuricemia

Twelve children had UA levels $\geq \bar{x} + 2s$. Except in one child, the concentrations of the other serum constituents were within the normal range. This child had the lowest GLUC level (4.55 mmol/l) and the highest levels of UA (0.402 mmol/l) and TC (7.5 mmol/l); however, his TC showed the usual distribution among the LPs (α-LP = 30 %, pre-β-LP=13 %, β-LP=55 %). Interestingly, this group shared its inverse reltationship of GLUC:UA ($r=-0.52$, $P<0.05$) with children exhibiting high levels of TC. This also tends to be the case in children with an increased $\beta:\alpha$-LP ratio, or high levels of TG and in growth-retarded, socially underprivileged children (Tab.6). Since these metabolic variables as well as hyperuricemia are recognized as being related to the risk of CHD (66,67), one might speculate that these 12 hyperuricemic children also carry a risk of the disease. However, whether or not the differences seen are the result of pathological alterations or differences in diet remains to be clarified.

Hypertriglyceridemia and hypo-α-lipoproteinemia

Eleven children (group 1) had TG levels $\geq \bar{x}+2s$, with a group mean twice normal (1.77 ± 0.38 mmol/l). The other variables tested were within the normal range including α-LP (1.17 ± 0.28 mmol/l = 85 % of normal). Another group of 12 children (group 2)(Tab. 7b) had α-LP levels $\leq \bar{x} - 1.5$ s (0.78 ± 0.09 mmol/l = 57 % of normal).

However, the other parameters measured were not clearly altered including TG (1.0±0.32 mmol/l = 20 % above normal), PC (2.09±0.40 mmol/l = 89 % of normal) and CE (3.31±0.69 mmol/l = 97 % of normal).

As shown in Tab.6, a moderate but significant correlation of TC:α-LP was seen in the reference sample group (r=0.38). A similar association was observed in group 1 (r=0.62), but was completely absent in group 2 (r=0), suggesting in hypo-α-lipoproteinemia a loss of any coordination between the two variables. Although the concentrations of PC and CE were not altered in group 2, a moderate but significant correlation of PC:CE was observed (r=0.57). One might speculate that this hints at a defense mechanism in the sense that the deposition of nonpolar CE might be rendered more difficult by a closer relation to polar PC (59). Whether or not the LCAT -reaction is involved (54) - despite markedly reduced levels of α-LP - remains to be clarified. An inverse relationship between HDL-TC and lipoprotein lipase activity has been reported and, also, that 70 % of people with low HDL-TC values have elevated TG levels (65,69). However, this inverse relation was only seen in our group 2, which had low levels of α-LP but relatively normal levels of TG (r = -0.69) (Tab. 6). On the other hand, group 1 - furnished with high levels of TG but normal levels of α-LP - showed no relation between these variables (r=0.14). These data suggest that additional mechanisms might be involved in the regulation of TG and α-LP levels, at least in young children.

Hper-α-lipoproteinemia

Twelve children had concentrations of α-LP $\geq \bar{x}+1.75$ s (2.10±0.17 mmol/l = 52 % above normal (Tab. 7c). Except in one child, the β:α-LP ratios varied within the lower limits of the normal range. Data obtained from this child (No. 229) were excluded from correlation analysis. In contrast to the group with hypolecithinemia (see below), PC of this group was positively correlated with

C, CE and β-LP, thus possibly rendering cholesterol deposition more difficult (59). We cannot tell whether these cases of hyper-α-lipoproteinemia are a familial (70,71) or reactive type (72).

Hypercholesterolemia and the increased $\beta:\alpha$-LP ratio

Twelve children had TC levels $\geq \bar{x} + 2s$ (Tab. 7d). However, a variable distribution of this TC among the LPs led to $\beta:\alpha$-LP ratios which varied within the normal limits, except in 2 children (No. 276 and 254) who had elevated values, and 2 other children (No.376 and 399) who had values within the lower normal range. Since elevated TC levels are associated with atherogenesis (25), 12 children would carry a risk of the disease. Since an elevated $\beta:\alpha$-LP ratio has been introduced as an indicator of the disease (73), only 2 children (No. 276 and 254) might be regarded as subjects at risk. Since a low $\beta:\alpha$-LP ratio may be related to prolonged longevity and decreased morbidity of the disease (71), 2 children (No. 399 and 376) might be protected, despite high levels of TC.

Since excess TC was due to elevated α-LP levels in 2 children (No. 376 and 399), their data were excluded from correlation analysis. As shown in Tab. 6, the remaining members of this group had nearly lost the association of CE:C (r=0.17), compared to the reference sample group. Furthermore, the complete loss of any association of TC: α-LP (r=0) seen in this group was also observed in hypolecithinemia (see below) and hypo-α-lipoproteinemia. Of all groups tested, only the present group showed a significant inverse association of $\beta : \alpha$-LP (r=-0.54).

The GLUC levels were not altered in this hypercholesterolemic group.(5.16±0.51 mmol/l). However, as seen in hyperglycemia, this group also had an inverse relation of GLUC:TC (r=-0.58). The negative correlation between TG:α-LP observed in hypo-α-lipoproteinemia was also found in this hypercholesterolemic group.

Another group of children was defined according to their $\beta : \alpha$-LP ratios (Tab. 7e). Of these 13 children, 11 had TC levels within the normal range, but 2 had high concentrations of TC (No. 254 and 276). Data obtained on these 2 children were excluded from correlation analysis. As shown in Tab. 6, $\beta : \alpha$-LP was positively correlated in this normocholesterolemic group (r=0.53); however, in the hypercholesterolemic group (Tab. 7d), these LPs were inversely correlated (r=-0.54). Furthermore, a weak but significant correlation PC: α-LP found in the reference sample group (r=0.40), was lost not only in this group with an increased $\beta : \alpha$-LP ratio but also in the groups with hyperglycemia and hypercholesterolemia.

Two types of metabolic patterns could be observed: One referring to hypercholesterolemia associated with normal $\beta : \alpha$-LP ratios, and another one exhibiting increased $\beta : \alpha$-LP ratios but normal TC levels. The pathophysiological significance of the results and their prognostic value remains to be elucidated.

Hypolecithinemia

Eight children had PC (lecithin) levels $\leq \bar{x} - 2s$ (1.57 mmol/l = 67 % of normal)(Tab. 7f) together with relatively low levels of PE, CE, C and α-LP (82 - 89 % of normal). Interestingly, the lowest PC level (No. 24) was associated with the highest $\beta : \alpha$-LP ratio. Correlation coefficients are shown in Tab. 6. Although the levels of α-LP were only moderately reduced in this group, the association of TC: α-LP was completely lost (r=0), a phenomenon which was also found in the group with hypo-α-lipoproteinemia and hypercholesterolemia. Furthermore, PC and PE were inversely related (r=-0.62). Since the levels of PE were reduced to a lesser extent (86 % of normal) than those of PC (67 % of normal), it is tempting to speculate that the primary defect might be an impaired transmethylation process (56,5 possibly due to folic acid deficiency. Moreover, the concentrations of C were moderately reduced (90 % of normal), compared to PC

(67 % of normal), thus causing a relative predominance of C over PC. Since it has been reported that the esterification of C via the LCAT reaction and accumulation of TC in the tissues is dependent on an appropriate PC:C ratio (74-76), a decrease of this ratio might hint at impaired TC clearance in this group. Hypolecithinemia seems to make elimination mechanisms for C, CE and β-LP less effective which appears to be reflected in the inverse association of PC with these metabolites. Experiments with human atherosclerotic lesions have shown that the solubilization of cholesterol crystals can be remarkably accelerated by the addition of PC (59). Accordingly, the inverse process might occur in PC deficiency seen in this group of children.

Provided vitamin deficiency is one causative factor for these processes, more attention should be payed to malnutrition. Indeed, malnutrition in childhood has been proposed as a risk factor in atherogenesis (77).

Occurrence of a double pre- β - LP band

Of the 335 children in the reference sample group, 7 (2.1 %) had a double pre-β-LP band. In all except one of these children, the other variable tested ranged within normal limits. This low frequency together with normal TC levels does not agree with findings in Swedish boys (16-17 yr) who exhibited a high frequency of this double pre-β-LP band (43 %) combined with a higher mean value of TC (73). The one exceptional child in our group had high GLUC levels and low concentrations of TC associated with an inversion of its LP-TC distribution pattern (see Tab. 7a, No. 5); this result was discussed above.

Overweight children

It has been reported from a pediatric study in Bogalusa (79) that the most obese children tended to have higher levels of TG, pre-β-LP and β-LP. However, this observation did not apply to our overweight children. As shown in Tab.2, their meanweight was 46 % above the mean value of the reference sample group. Nevertheless, this obese group had normal values for all metabolic parameters estimated, except for TC, which was significantly diminished due to a decrease in β-LP (Tab. 8). Correlation analysis of various metabolic pairs yielded nearly the same results as in the reference sample group

Obesity in adults is associated with both increased cholesterol synthesis and enhanced cholesterol elimination mechanisms. This may explain the fact that obese subjects usually have normal or even subnormal TC levels(80,81). Furthermore, an alteration of the TC distribution pattern has been observed: Overweight healthy persons differed from the rest of the population by having higher VLDL-TC and lower HDL-TC levels (30). In our group of children, however, an isolated decrease of β-LP was seen, suggesting that the primary response to enhanced TC synthesis might be enhanced activity of the β-LP clearance mechanisms at the receptor sites in the tissues (82). Thus, this isolated decrease of β-LP might be interpreted as an early indicator of metabolic disorders in obesity of young children, such as in our group (3-7 yr). The changes observed in older children (5-14 yr)(79) and in adults may reflect advanced disorders.

S o c i a l l y u n d e r p r i v i l e g e d c h i l d r e n

Among the 117 socially underprivileged children, 93 were normal according to the anthropometric criteria (Tab. 2), but 14 children showed retarded growth and the remaining children were either overweight or taller than normal. In this report, only the data on the normal (n=93) and the growth-retarded children (n=14) will be discussed.

Normal growth

As shown in Tab. 8, the levels of GLUC, TG, PC, C, CE, TC, α-LP and pre-β-LP were significantly reduced. Similar results have been reported for protein malnutrion syndromes such as kwashiorkor.

Hypoglycemia, for example, may reflect an inappropriate situation in nutrient intake and/or absorption; in the supply of GLUC from the hepatic glycogen reserves; in carbohydrate metabolism such as a defect in gluconeogenesis or insulin hypersensitivity (84-86).

The PE concentrations were normal, while PC was markedly diminished; this was also reflected in a reduced PC:PE ratio . Both a reduced dietary intake of PC and impaired methylation due to vitamin deficiency may be causative factors(56,57,87,88). A similar phenomenon was observed in our sub-group with hypolecithinemia (Tab. 7f). Reduced levels have also been reported for TG and VLDL (89) as well as for TC (90). These data parallel our findings of reduced TG, TC and pre-β-LP concentrations. Since release of pre-β-LP from the liver may be reduced in such cases (89) this might also be true for α-LP, which was also diminished in our children. This reduced α-LP is responsible for a significant increase of the β : α-LP ratio (Tab. 8; this ratio was discussed above in the chapter on sub-groups).

Correlation analysis of various metabolic pairs (Tab. 6) revealed only one difference between the reference sample group and these socially underprivileged children, namely an inverse relationship of TG: α-LP, as was also seen in the sub-groups with hypercholesterolemia and hypo-α-lipoproteinemia (see above) as well as in the

socially underprivileged group with retarded growth (see below).

Retarded growth

As did the children in the socially underprivileged group with normal growth, this growth-retarded sub-group had metabolite concentrations in the lower part of the normal range. The sole exception is β-LP, which tended to lie in the upper normal range. This together with relatively low α-LP levels leads to altered $\beta : \alpha$-LP ratios: Of the 14 children in this group, 7 had a $\beta : \alpha$-LP ratio in the upper normal range and 4 had one above normal (Tab. 9).

Correlation analysis (Tab. 6) showed a complete loss of the regulation of CE:C (r=0) - in common with the sub-group exhibiting hypercholesterolemia (see above). Since it has been reported that severe protein malnutrition can be associated with fatal hypoglycemia (84) and impaired lipoproteinlipase activity (90) the results obtained on our 14 growth-retarded children may reflect advanced metabolic alterations: Low GLUC levels were directly related to low α-LP levels and inversely related to the levels of TG. Moreover, in common with the sub-group with hypercholesterolemia and hypo-α-lipoproteinemia as well as the socially underprivileged children with normal growth, this growth-retarded group also showed an inverse relation of TG: α-LP.

These data suggest that children living under negative socio-economic conditions may exhibit normal growth - despite significant alterations in metabolite concentrations typical of protein malnutrition. However, although these metabolite concentrations did not unequivocally differ within the two socially underprivileged groups a dysregulation between metabolic pairs seems to be reflected in retarded growth. Furthermore, several metabolic phenomena which are currently considered to be related to the risk of atherogenesis, were also identified in these socially underprivileged children. This

raises the question whether these children do not also run the risk of contracting CHD. Possibly, poor living conditions in childhood might favor development of the disease (77) and without any doubt, early diagnosis is essential (91).

C O N C L U S I O N S

Primary prevention of CHD includes the early detection of specific risk indicators of the disease. This study has provided a field test of a new methodology found to be adequate and appro - priate for the identification of metabolic disorders recognized in adults to be related to CHD, yet detectable in apparently healthy young children. Results obtained on special sub-groups, obese as well as socially underprivileged children suggest that multiple factors may contribute to the risk of CHD: Not only altered con - centrations of metabolites, but also the disappearance or inversion of coupled control mechanisms. The data clearly demonstrate that the appropriate information can be obtained from a detailed analysis and careful interpretation of metabolic patterns.

We have started to examine the kin of children who exhibited metabolic abnormalities. Preliminary results strongly suggest that our approach to identifying subjects at potential risk can be a valuable step towards primary prevention of CHD, as recommended by the World Health Organization (23,92). An extension of the present pilot study to longitudinal studies is planned for the near future.

A C K N O W L E G E M E N T S

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L E G E N D S

TABLE 1

LIPID CONCENTRATIONS IN CAPILLARY SERUM OF THE REFERENCE SAMPLE GROUP (n=335) AS DETERMINED BY TWO ANALYSTS USING TWO MICROMETHODS

TABLE 2

ANTHROPOMETRIC DATA AND BLOOD PRESSURE

TABLE 3

REFERENCE VALUES (n=335)

TABLE 4

SYNOPSIS OF DATA REPORTED BY OTHER INVESTIGATORS
Data of the present study refer to capillary blood serum.

TABLE 5

REFERENCE SAMPLE GROUP: RATIOS AND CORRELATION ANALYSIS OF METABOLIC PAIRS

TABLE 6

CORRELATION ANALYSIS OF METABOLIC PAIRS IN VARIOUS GROUPS
Sub-groups and socially underprivileged children are compared with the reference sample group. Data indicate correlation coefficients; level of significance (numbers in parenthesis): a=$P < 0.0005$, b=$P < 0.0025$, c=$P < 0.005$, d=$P < 0.01$, e=$P < 0.025$, f=$P < 0.05$, g=$P < 0.10$.

TABLE 7 a

SUB-GROUP WITH HYPERGLYCEMIA
Data indicate standard deviations from the mean of the reference sample group.

TABLE 7 b

SUB-GROUP WITH HYPO - α - LIPOPROTEINEMIA
Text see Table 7a.

TABLE 7 c

SUB-GROUP WITH HYPER - α - LIPOPROTEINEMIA
Text see Table 7 a.

TABLE 7 d

SUB-GROUP WITH HYPERCHOLESTEROLEMIA
Text see Table 7 a.

TABLE 7 e

SUB-GROUP WITH AN INCREASED β : α - LP RATIO
Text see Table 7 a.

TABLE 7 f

SUB-GROUP WITH HYPOLECITHINEMIA
Text see Table 7 a.

TABLE 8

COMPARISON OF OVERWEIGHT AND SOCIALLY UNDERPRIVILEGED CHILDREN WITH THE REFERENCE SAMPLE GROUP
Data indicate percentiles.

TABLE 9

SOCIALLY UNDERPRIVILEGED CHILDREN WITH RETARDED GROWTH
Data indicate standard deviations from the mean of the reference sample group.

Figs. 1 a - d

Frequency distribution of metabolites.

Table 1

Lipids of capillary serum (mmol/l)	Enzymatic determination		HPTLC
	analyst 1	analyst 2	
TC	4.62 ± 0.74	4.60 ± 0.74	4.51 ± 0.75
CE	3.38 ± 0.54	3.41 ± 0.56	3.23 ± 0.55
C	1.24 ± 0.26	1.24 ± 0.26	1.27 ± 0.23
TG	0.82 ± 0.32	0.83 ± 0.32	0.88 ± 0.32

Table 2

	$\bar{x} \pm 2s_x$	Percentiles							
		Min.	2.5	25	50	75	90	97.5	Max.
Reference sample group (n=335)									
Age (yr)	5.05±1.98	3.00	3.25	4.35	5.00	5.75	6.20	6.90	8.70
Height (cm)	112 ±14.8	92	98	106	113	117	122	126	135
Weight (kg)	18.8±6.0	12	13	16	19	20	22	24	30
Blood pressure (mm Hg)(syst.).	94 ±24	60	70	85	90	99	108	115	130
(diast.)	60 ±18	35	40	53	59	63	70	80	85
Overweight (n=22)									
Age (yr)	5.45±2.16	3.80	3.85	4.17	2.25	5.75	6.10	6.75	7.75
Height (cm)	115 ±15	99	99	110	116	119	123	126	129
Weight (kg)	27.4±10	22	22	24	26	28	30	35	45
Blood presssure(mmHg)(syst.)	97 ±24	75	75	87	96	103	110	116	120
(diast.)	61 ±16	50	50	55	58	60	68	70	80
Socially underpriv. (n=96)									
Age (yr)	5.50±3.0	2.42	2.45	4.25	5.25	6.25	7.00	8.30	8.80
Heigt (cm)	112 ±37	88	93	104	112	119	123	130	136
Weight (kg)	18.5±6.4	10	12	16	18	20	22	24	26
Blood pressure(mmHg)(syst.)	89 ±24	70	70	75	87	95	105	115	120
(diast.)	55 ±17	40	40	47	55	58	65	70	80

Table 3

Variable	Type of distribution	$\bar{x} \pm 2s_x$	Percentiles							
			Min.	2.5	25.	50	75	90	97.5	Max.
Concentration (mmol/l)										
G L U C	normal	5.19 ± 1.18	3.55	4.06	4.78	5.06	5.50	5.89	6.33	7.78
U A	normal	0.218±0.106	0.030	0.115	0.180	0.210	0.245	0.280	0.330	0.400
T G	normal	0.83 ± 0.64	0.12	0.25	0.58	0.83	1.00	1.22	1.57	2.01
P C	normal	2.35 ± 0.72	1.40	1.63	2.13	2.33	2.56	2.84	3.09	3.50
P E	normal	0.50 ± 0.17	0.32	0.35	0.44	0.50	0.55	0.61	0.70	0.88
C	normal	1.24 ± 0.52	0.61	0.78	1.05	1.21	1.36	1.56	1.86	2.27
C E	normal	3.41 ± 1.12	2.04	2.35	3.04	3.39	3.74	4.05	4.72	5.23
T C	normal	4.65 ± 1.46	2.79	3.18	4.08	4.56	4.99	5.38	6.45	7.50
α - L P	normal	1.38 ± 0.60	0.58	0.80	1.15	1.34	1.55	1.75	1.98	2.54
pre - β - L P	normal	0.61 ± 0.47	0.12	0.22	0.42	0.58	0.71	0.90	1.22	1.43
β - L P	normal	2.52 ± 1.16	1.17	1.51	2.11	2.50	2.82	3.24	3.88	5.58
Percent distribution(%)										
α - L P	normal	30.0 ± 12.8	11.6	18.1	25.7	29.4	34.3	37.6	43.9	62.7
pre - β - L P	normal	13.2 ± 9.7	2.7	5.3	9.7	12.6	15.9	19.5	24.8	36.3
β - L P	normal	54.8 ± 15.6	24.0	37.0	50.2	55.1	59.5	63.0	68.6	85.3

Table 4

City, country (reference)	Sex	Age (yr)	T G	T C	H D L, α-LP	V L D L, pre-β-LP	L D L, β-LP	LDL / HDL	T C / HDL
Central European cities									
Aalborg, Denmark (45)	boys	6-10	0.77±0.22	5.04±0.89	-	-	-	-	-
Wageningen, The Netherlands (46)	boys	7-8	-	4.27±0.10	1.33±0.05	-	-	-	3.2
Duesseldorf, Germany (this study)	boys & girls	3-7	0.83±0.32	4.65±0.73	1.38±0.30	0.61±0.23	2.52±0.58	1.9	3.2
Geneva, Switzerland (47)	boys	8-9	0.57	4.80±0.70	1.66±0.24	0.06	2.64±0.56	1.6	2.9
	girls	8-9	0.60	5.06±0.80	1.61±0.33	0.08	2.72±0.61	1.9	3.1
Vienna, Austria (48)	boys & girls	5-13	0.96±0.28	4.65±0.76	1.44±0.40	0.34±0.29	2.70±0.75	1.9	3.2
Cittadella area, North Italy (49)	boys & girls	7-14	0.81±0.55	3.99±0.96	1.29±0.38	0.27±0.43	2.49±0.78	1.9	3.1
United States (North-East, East, South-East)									
Rochester, Minn. (50)	boys	6-10	0.59±0.25	4.12±0.52	1.37±0.15	0.15±0.15	2.69±0.47	2.0	3.0
	girls	6-10	0.65±0.29	4.15±0.62	1.30±0.21	0.21±0.15	2.77±0.47	2.1	3.2
Muscatine, Iowa (51)	boys	6-18	0.81	4.22	1.30	0.21	2.67	2.1	3.3
Cincinnati, Ohio (52)	boys	6-7	0.57±0.18	4.09±0.54	1.45±0.28	-	2.44±0.54	1.7	2.8
	girls	6-7	0.81±0.40	4.17±0.41	1.27±0.23	-	2.62±0.49	2.1	3.3
Bethesda, M.D. (32)	boys & girls	1-19	0.74(.1-1.6)	4.53±0.73	1.35±0.34	0.31±0.21	2.67±0.70	2.0	3.3
Bogalusa, Louis. (53)	boys & girls	3-6	0.72	4.07	1.55	0.16	2.36	1.5	2.6

Table 5

Ratio	Type of distribution	$\bar{x} \pm 2s_x$	Percentiles								Correlation		
			Min.	2.5	25	50	75	90	97.5	Max.	y=bx + a	r	P
TC : C	normal	3.80 ± 0.88	2.76	3.01	3.53	3.77	4.03	4.32	4.77	5.51	y=0.29x-0.09	0.85	< .0005
TC : CE	not norm.	1.38 ± 0.14	1.24	1.24	1.29	1.34	1.39	1.44	1.53	1.57	y=0.68x+0.26	0.91	< .0005
CE : C	normal	2.80 ± 0.88	1.67	1.97	2.52	2.77	3.02	3.32	3.76	4.51	y=0.28x+0.33	0.51	< .0005
TC : β-LP	not norm.	1.87 ± 0.62	1.17	1.45	1.68	1.81	1.98	2.18	2.50	4.17	y=0.57x-0.13	0.71	< .0005
TC : α-LP	not norm.	3.49 ± 1.64	1.60	2.28	2.91	3.39	3.89	4.42	5.51	8.61	y=0.15x+0.66	0.38	< .0005
β : α-LP	not norm.	1.86 ± 1.24	0.48	1.00	1.50	1.87	2.26	2.64	3.56	7.34	-	0.22	N.S.
PC : PE	normal	4.77 ± 1.58	2.71	3.25	4.24	4.69	5.15	5.75	6.51	8.46	y=0.13x+0.20	0.51	< .0005
PC : α-LP	not norm.	1.79 ± 0.84	0.84	1.17	1.52	1.74	1.96	2.28	2.78	3.65	y=0.34x+0.56	0.40	< .0005

No correlation:

GLUC: pre-β-LP, GLUC:β-LP, GLUC:α-LP, GLUC:TC, GLUC:UA, GLUC:TG, TG:α-LP, TG:pre-β-LP, TG:C, TG:UA, TC:UA, β-LP:UA, α-LP:UA, PC:CE, PC:C, PC:β-LP, β:pre-β-LP, α:pre-β-LP.

Table 6

	Reference sample group	GLUC $\geq \bar{x}+2s$	T G $\geq \bar{x}+2s$	P C $\leq \bar{x}-2s$	T C $\geq \bar{x}+2s$	α-LP $\geq \bar{x}+1.75s$	α-LP $\leq \bar{x}-1.5s$	$\beta:\alpha$-LP $\geq \bar{x}+2s$	Soc.underpriv. normal growth	Soc.underpriv. retarded growth
T C :C	0.85(a)	0.95(a)	0.93(a)	0.92(a)	0.82(a)	0.91(a)	0.96(a)	0.95(a)	0.83(a)	0.45(g)
T C :C E	0.91(a)	0.99(a)	0.98(a)	0.99(a)	0.67(c)	0.96(a)	0.99(a)	0.99(a)	0.97(a)	0.93(a)
C E :C	0.51(a)	0.89(a)	0.84(c)	0.84(c)	0.17	0.79(d)	0.93(a)	0.91(a)	0.67(a)	0
T C : β-LP	0.78(a)	0.88(b)	0.83(b)	0.92(a)	0.67(d)	0.57(f)	0.95(a)	0.54(g)	0.82(a)	0.68(c)
T C : α-LP	0.38(a)	0.40	0.62(e)	0	0	0.44	0	0.28	0.36(a)	0.40
β : α-LP	-0.22	0.20	0	-0.35	-0.54(f)	-0.35	0	0.53(f)	0	0.10
P C :P E	0.51(a)	0.37	0.59(e)	-0.62(f)	0.20	0.30	0.36	0.66(d)	0.62(a)	0.64(d)
P C :C	0.25(f)	0.20	0.53(g)	-0.75(e)	0.10	0.51(d)	0.40	0.33	0.45(a)	0.27
P C :C E	0.20	0.49	0.10	-0.69(f)	0.36	0.69(d)	0.57(f)	0	0.30(b)	0.22
P C : β-LP	0.25(f)	0.14	0.37	-0.73(e)	0.22	0.62(e)	0.45(g)	0.34	0.36(a)	0.10
P C : α-LP	0.40(c)	0	0.44	0.50	0.10	0.49(g)	-0.33	0.14	0.36(a)	0.87(a)
GLUC :T C	0.10	-0.56(f)	0.27	0.46	-0.58(e)	0	0.10	0	0	0
GLUC : β-LP	0.10	-0.66(e)	-0.50(e)	0.64(e)	-0.39	0	0.10	-0.10	0	0.27
GLUC :pre-β-LP	0.10	0.75(d)	0.36	0.45	0.27	0.14	0	0.17	0	-0.44(g)
GLUC : α-LP	0.14	-0.17	0.10	-0.57(g)	0.22	0	0.25	0	0.10	0.64(d)
GLUC :U A	0.17	0.36	-0.52(g)	0.10	-0.57(f)	0.20	0.37	-0.53(g)	0.10	-0.46(g)
GLUC :T G	0	-0.30	0.10	0.28	0.10	0.25	0.32	0.14	0	-0.59(e)
T G : α-LP	0.22	-0.50(g)	0.14	0.14	-0.57(e)	0.14	-0.69(c)	0	-0.35(a)	-0.49(f)
U A : β-LP	0.27(f)	0.45	0.14	0.10	0.25	0.51(g)	0.37	0.28	0	0

Table 7 a

No.	G L U C	T C	β - LP	pre-β-LP	α-LP	T G	U A	β : α-LP
370	+ 2.0	+ 2.7	+ 1.0	- 0.8	+ 1.3	- 0.6	+ 0.2	- 0.4
121	+ 2.0	- 1.4	- 1.1	- 0.4	- 1.3	+ 0.6	+ 1.1	0
402	+ 2.0	- 0.4	- 0.9	0	+ 0.9	- 0.9	+ 0.4	- 1.2
1	+ 2.1	+ 0.5	- 0.2	+ 0.8	- 0.2	- 1.8	+ 1.5	- 0.1
13	+ 2.1	- 0.3	0	+ 1.1	- 1.2	+ 0.6	0	+ 1.0
401	+ 2.1	0	+ 0.2	0	- 0.8	0	- 0.5	+ 0.6
6	+ 2.5	+ 0.4	+ 0.2	+ 1.3	- 0.9	+ 0.1	0	+ 0.6
233	+ 2.5	- 1.4	- 1.5	+ 0.4	- 0.1	+ 0.4	- 0.2	- 1.2
344	+ 3.6	- 1.3	- 1.1	+ 0.5	- 0.4	- 0.9	0	- 0.8
5	+ 4.4	- 1.5	- 2.2	+ 2.9	- 0.6	- 0.9	+ 1.9	- 1.5

Table 7 b

No.	α-LP	β-LP	β:α-LP	T C	T G	P C
24	-1.5	+1.2	+3.0	+0.8	+0.5	-2.5
443	-1.5	+1.4	+2.9	-0.2	+0.3	-0.3
99	-1.7	-0.9	+0.8	-1.7	+0.4	-1.3
305	-1.7	-0.9	+0.6	-1.3	+0.1	-1.3
33	-1.8	-0.3	+1.3	-1.3	-0.6	-2.2
42	-1.8	+0.7	+2.8	-0.3	+0.3	-1.7
442	-1.8	+0.6	+2.7	-0.4	-0.6	0
262	-1.9	-0.3	+1.7	-0.2	+0.1	+1.3
276	-1.9	+5.1	+8.8	+2.3	+1.0	+0.7
261	-2.1	+2.3	+5.9	+0.8	+2.3	+0.2
306	-2.2	+0.9	+4.2	+0.4	+0.5	0
347	-2.4	-1.0	+2.2	-1.7	+2.8	-1.2

Table 7 c

No.	α-LP	β-LP	β:α-LP	T C	T G	P C
74	+1.8	-0.8	-1.5	-0.6	-0.7	+0.8
365	+1.8	-0.2	-1.2	+0.4	-0.8	-0.4
28	+1.8	-1.3	-1.8	+1.4	+1.5	+0.6
408	+1.8	+0.4	-0.9	+1.0	-1.6	+0.9
203	+1.9	-1.2	-1.7	+1.0	-1.0	+0.4
229	+1.9	+2.7	+1.9	+4.0	-1.0	+2.0
209	+2.1	0	-1.2	+1.6	+0.3	+2.0
376	+2.1	+0.9	-0.8	+2.4	+0.9	+1.6
371	+2.3	-0.3	-1.4	+0.4	-1.1	+0.4
393	+2.6	-0.3	-1.5	+0.6	+0.4	+0.8
400	+2.6	-0.5	-1.6	+0.3	-1.4	+0.9
399	+3.5	+0.7	-1.3	+2.9	+0.8	+2.4

Table 7 d

No.	TC	β - LP	pre-β-LP	α -LP	β : α-LP	TG	PC	UA	GLUC
226	+ 2.1	+ 2.4	- 0.3	+ 0.6	+ 0.9	+ 0.4	+ 2.4	+ 0.4	+0.1
51	+ 2.4	+ 2.0	+ 0.4	+ 0.7	+ 0.6	+ 0.8	+ 0.9	- 1.9	+1.2
376	+ 2.4	+ 0.9	+ 0.7	+ 2.1	- 0.8	+ 0.9	+ 1.6	-	+1.4
377	+ 2.5	+ 2.3	+ 0.2	+ 1.6	+ 0.2	- 0.6	+ 1.3	-	+0.5
399	+ 2.6	+ 0.7	+ 1.0	+ 3.5	- 1.3	- 0.8	+ 2.4	+ 0.3	+0.6
276	+ 2.7	+ 5.1	- 0.6	- 1.9	+ 8.8	+ 1.0	+ 0.7	+ 1.5	+0.3
202	+ 2.7	+ 1.4	+ 3.1	+ 0.5	+ 0.3	+ 1.3	+ 0.4	+ 0.8	-0.1
38	+ 3.0	+ 2.7	- 0.4	+ 1.0	+ 0.7	0	+ 0.8	- 1.2	+0.1
253	+ 3.1	+ 3.0	+ 1.1	+ 1.6	+ 0.5	- 0.3	+ 0.4	+ 0.5	-1.5
26	+ 3.2	+ 2.3	+ 3.3	+ 0.1	+ 1.3	+ 3.5	+ 0.6	- 1.4	-0.1
254	+ 3.3	+ 3.0	+ 1.4	- 0.3	+ 2.3	+ 0.5	+ 2.6	+ 1.5	-1.7
229	+ 4.0	+ 2.7	+ 1.1	+ 1.9	+ 0.2	- 1.0	+ 2.0	+ 3.5	-1.1

Table 7 e

No.	β :α-LP	β-LP	α-LP	T C	T G	P C	GLUC	U A
386	+2.1	+2.1	-0.7	+1.5	+1.3	-0.5	+1.4	-0.7
254	+2.3	+3.0	-0.3	+3.3	+.05	+.26	-1.7	+1.5
67	+2.5	+2.3	-0.8	+0.1	+.0.7	+1.8	-0.3	-
267	+2.7	+1.6	-1.3	+0.1	-0.3	-0.8	-2.2	+0.7
442	+2.7	+0.6	-1.8	-0.4	-0.6	+0.1	-0.3	--
42	+2.8	+0.7	-1.8	-0.3	+0.3	-1.7	+0.4	-2.1
443	+2.9	+1.4	-1.5	-0.2	+0.3	-0.3	-0.6	+0.4
70	+2.9	+1.0	-1.7	+0.2	+0.1	+0.9	-0.5	+1.9
24	+3.0	+1.2	-1.5	+0.8	+0.5	-2.5	+1.0	0
403	+3.2	+1.5	-1.3	+0.2	-0.8	+0.1	+1.6	-1.5
306	+4.2	+0.9	-2.2	+0.4	+0.5	-0.1	+0.1	0
261	+5.9	+2.3	-2.1	+0.8	+2.3	+0.2	-1.4	+0.9
276	+8.8	+5.1	-1.9	+2.7	+1.0	+0.7	+0.3	+1.5

Table 7 f

No.	P C	P E	C E	C	β-LP	α-LP	β : α-LP
469	-2.0	-0.4	-1.4	-0.6	-0.8	-0.4	-0.6
36	-2.1	-1.2	-0.8	-0.9	-0.2	-0.6	+0.2
192	-2.1	-1.3	-1.1	-0.7	-1.1	0	-1.0
354	-2.2	-1.7	-1.6	-1.7	-1.2	-0.9	-0.5
33	-2.2	-1.9	-1.4	-0.7	-0.3	-1.8	+1.3
35	-2.2	-0.2	-0.2	-1.9	0	0	-0.2
22	-2.3	-0.1	-1.4	-0.4	+0.7	-1.1	+0.3
24	-2.5	+0.4	+0.5	+0.9	+1.2	-1.5	+3.0

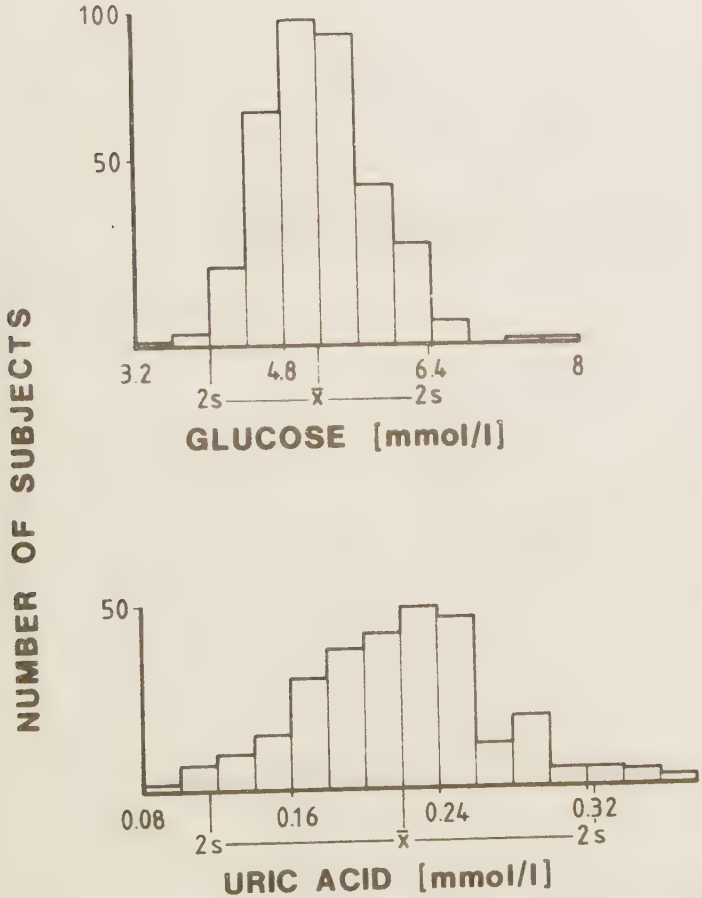
Table 8

Variable	Reference sample			Overweight				Socially underprivileged			
	5	50	95	5	50	95	P	5	50	95	P
Concentration (mmol/l)											
G L U C	4.06	5.06	6.33	4.11	5.17	6.11	N.S.	3.33	4.67	5.44	< 0.0005
U A	0.130	0.215	0.310	0.120	0.210	0.260	N.S.	0.130	0.225	0.290	N.S.
T G	0.32	0.83	1.40	0.19	0.66	1.40	N.S.	0.24	0.60	1.26	< 0.0005
P C	1.75	2.33	2.96	1.79	2.35	2.62	N.S.	1.60	2.08	2.72	< 0.0005
P E	0.37	0.49	0.66	0.32	0.48	0.59	N.S.	0.34	0.49	0.65	N.S.
C	0.85	1.21	1.73	0.90	1.08	1.34	N.S.	0.75	1.11	1.47	< 0.0005
C E	2.53	3.39	4.25	2.45	3.09	4.15	N.S.	2.26	3.03	3.77	< 0.0005
T C	3.45	4.56	5.73	3.31	4,25	5.31	< 0.05	3.10	4.09	5.11	< 0.0005
α - L P	0.91	1.34	1.92	0.86	1.30	1.75	N.S.	0.70	1.19	1.80	< 0.0005
pre-β - L P	0.27	0.58	1.05	0.22	0.48	0.94	N.S.	0.21	0.41	0.77	< 0.0005
β - L P	1.62	2.50	3.56	1.20	2.24	3.37	< 0.05	1.37	2.35	3.23	N.S.
Percent distribution(%)											
α - L P	20.8	29.4	40.4	18.3	32.0	37.8	N.S.	17.6	29.7	41.1	N.S.
pre-β - L P	6.9	12.6	22.0	6.6	10.7	18.3	N.S.	5.3	10.3	18.7	< 0.0005
β - L P	41.9	55.1	66.0	30.1	54.0	63.5	N.S.	41.0	59.1	69.4	< 0.0005
Ratios											
β : α - L P	1.1	1.9	3.0	0.9	1.7	2.7	N.S.	0.9	2.1	3.7	< 0.05
PC : α - L P	1.3	1.7	2.5	1.0	1.8	2.2	N.S.	1.1	1.7	2.7	N.S.
PC : PE	3.6	4.7	6.0	3.8	4.6	6.2	N.S.	3.3	4.2	5.3	< 0.0005
TC : C	3.1	3.8	4.6	3.2	3.9	4.5	N.S.	3.1	3.7	4.4	N.S.

Tab. 9

No.	β : α-LP	β-LP	α-LP	T C	P C	P E	T G	GLUC
553	- 0.9	- 0.5	+ 0.6	- 0.5	+ 0.3	- 0.1	- 0.2	- 0.7
566	- 0.1	- 0.1	- 0.3	- 0.6	- 0.1	- 0.3	- 1.0	- 0.9
572	- 0.1	- 0.1	- 0.3	- 0.8	+ 0.8	+ 1.8	+ 0.1	- 0.5
494	+ 0.4	+ 0.5	- 0.3	- 0.6	+ 0.5	+ 0.9	- 0.8	+ 0.9
562	+ 0.5	+ 0.1	- 0.8	- 0.6	- 1.0	+ 0.1	- 1.0	+ 0.1
551	+ 0.7	+ 0.5	- 0.6	- 0.4	+ 0.3	- 0.7	- 0.4	+ 0.3
138	+ 0.9	+ 0.5	- 1.5	- 0.5	- 0.4	+ 0.7	+ 1.7	- 2.6
557	+ 1.0	+ 1.7	- 0.1	+ 1.2	+ 1.0	+ 0.1	- 0.7	- 1.8
568	+ 1.2	+ 1.2	- 0.6	+ 0.7	- 0.3	- 0.1	- 0.5	+ 0.5
137	+ 1.8	+ 0.7	- 1.3	+ 0.4	-	- 1.3	+ 1.1	- 3.1
155	+ 3.6	+ 0.5	- 2.1	- 0.5	- 2.3	- 1.0	+ 0.9	- 1.4
146	+ 4.1	- 0.6	- 2.7	- 2.0	- 1.9	- 0.1	- 0.4	- 2.6
506	+ 4.7	+ 2.2	- 1.8	- 0.2	- 2.1	- 0.9	0	- 3.9
141	+ 4.7	+ 1.0	- 2.2	- 0.4	- 1.5	- 1.1	+ 0.8	- 2.7

Figs. 1a - d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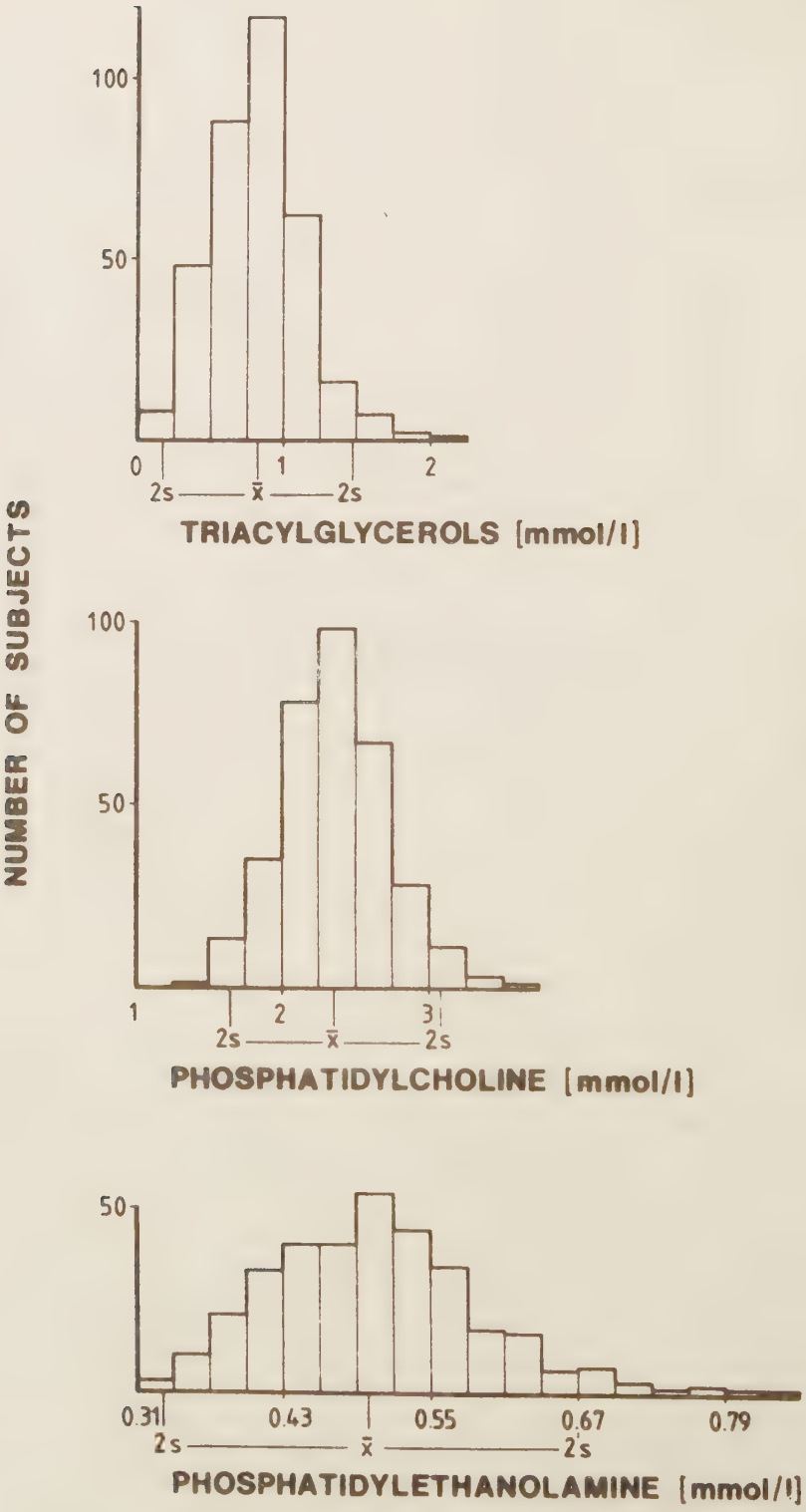
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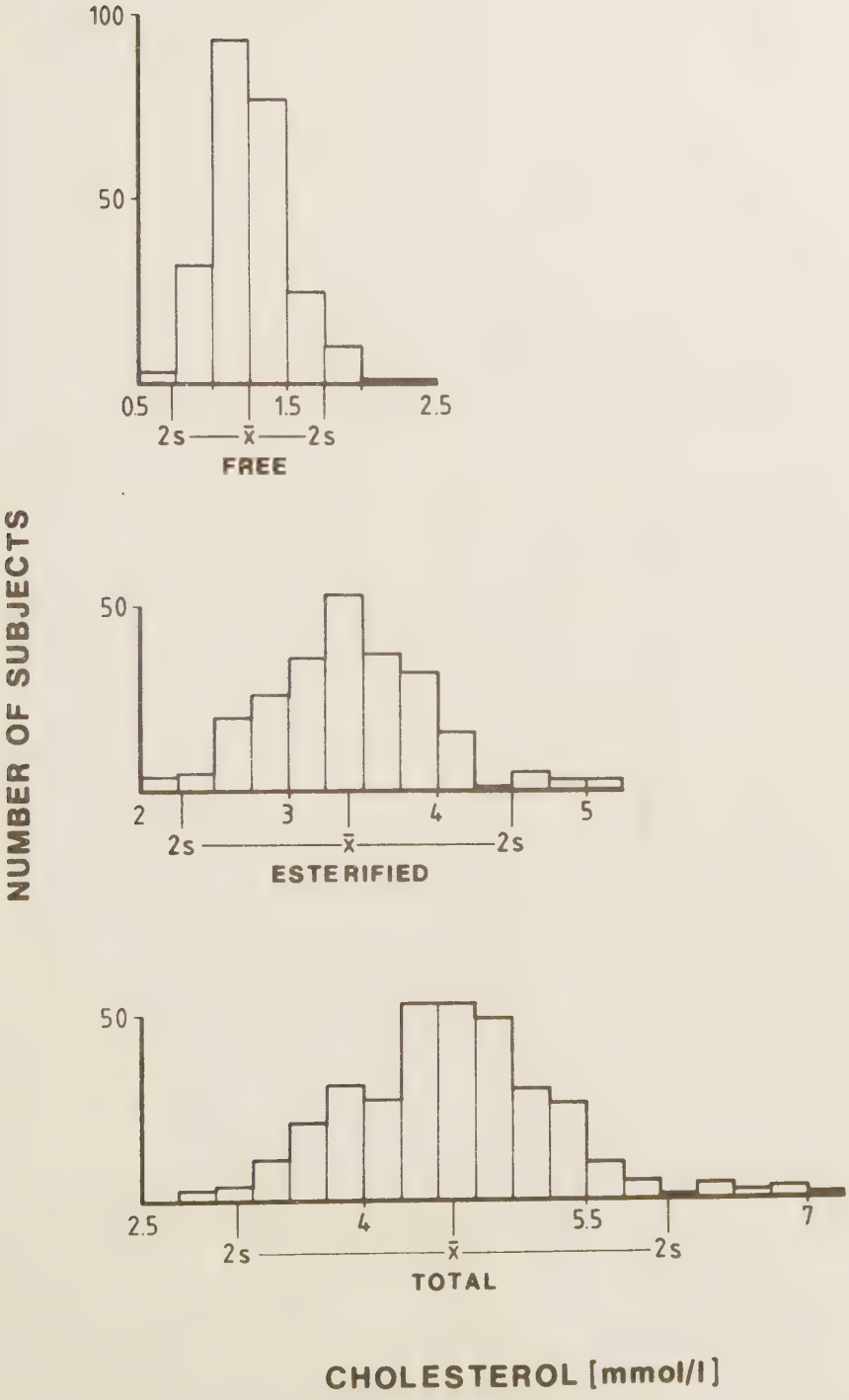
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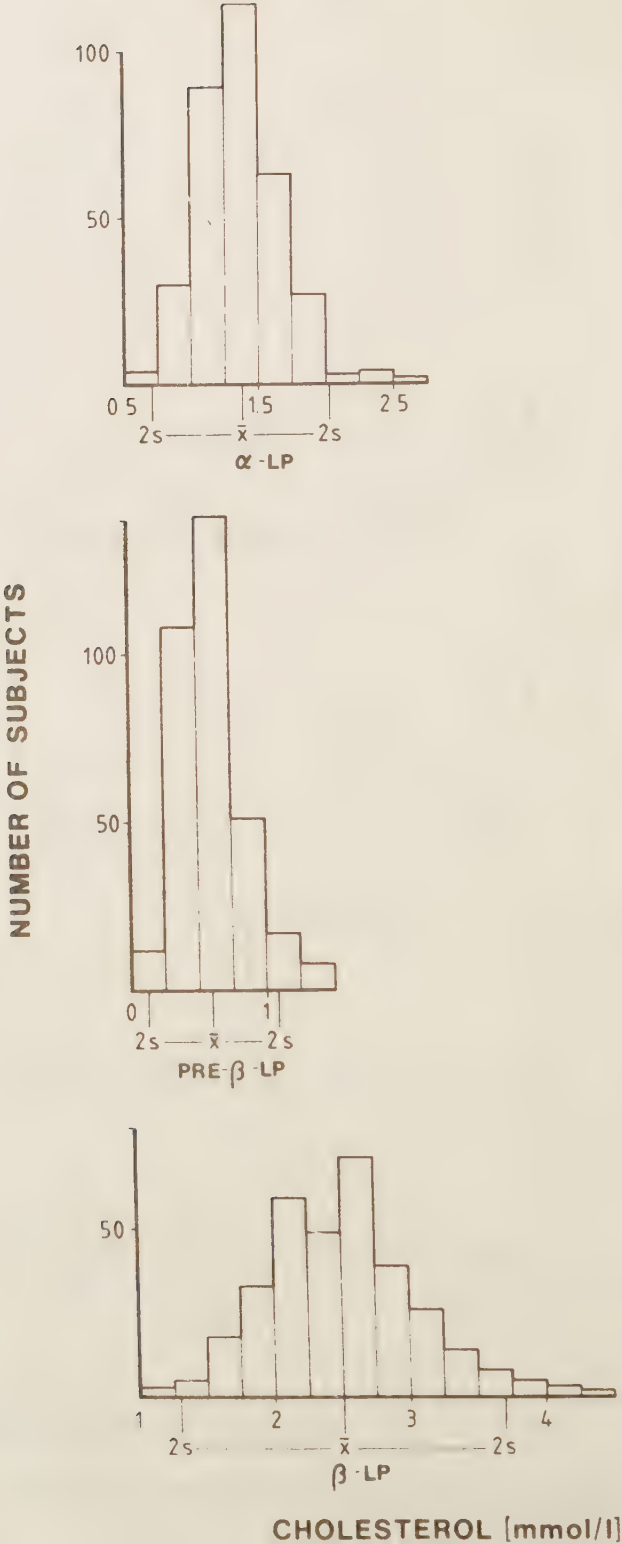
TOTAL
CHOLESTEROL [mmol/l]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β -LP
CHOLESTEROL [mmol/l]

LEBENSLAUF

Ich, Barbara Heller, wurde am 23. September 1954 als Tochter der Assistenzärztin Lotte Heller, geb. Brummert, und des Assistenzarztes Heinz-Bjarne Heller in Bielefeld geboren. Nach dem Umzug 1957 nach Gütersloh besuchte ich dort zunächst die Grundschule, später das Städtisch-Neusprachliche Gymnasium, wo ich im Mai 1973 das Abitur ablegte. Zum anschließenden Wintersemester 73/74 Beginn des Studiums der Humanmedizin an der Ruhruniversität Bochum, dort im März 1976 Bestehen der Ärztlichen Vorprüfung und Wechsel an die Universität Düsseldorf. Im Frühjahr 1977 Ablegen des Ersten Abschnittes der Ärztlichen Prüfung, im Frühjahr 1979 Bestehen des Zweiten Abschnittes der Ärztlichen Prüfung. Danach Wechsel an die Universität Essen. Ableistung des Praktischen Jahres am Elisabeth-Krankenhaus Essen und im April 1980 Ablegen des Dritten Abschnittes der Ärztlichen Prüfung. Seit Juli 1980 tätig als Assistenzärztin im Bereich der Medizinischen Klinik der Krankenanstalten Sarepta in Bielefeld - Bethel.

LEBENSLAUF

Ich, Peter Weiss, wurde am 7. Dez. 1954 als Sohn des Kammermusikers Günter Weiss und seiner Ehefrau, der Hausfrau Christel Weiss, in Gelsenkirchen geboren.
Von 1961 bis 1965 besuchte ich die Grundschule in Bochum 1975 wechselte ich an das Staatliche Gymnasium Bochum, wo ich 1973 meine Schulausbildung mit dem Abitur abschloß.
Zum Wintersemester 1973/74 nahm ich das Studium der Medizin an der Ruhruniversität Bochum auf. Nach Bestehen der Ärztlichen Vorprüfung im März 1976 wechselte ich an die Universität Düsseldorf, an der ich im März 1977 den 1. Abschnitt und im März 1979 den 2. Abschnitt der Ärztlichen Prüfung ablegte.
Da in den Düsseldorfer Lehrkrankenhäusern zum Sommersemester 1979 nicht genügend Ausbildungsplätze für das Praktische Jahr zur Verfügung standen, wechselte ich zur Universität Essen, an der ich mein Praktisches Jahr im Elisabeth-Krankenhaus ableistete. Im April 1980 legte ich dann den 3. Abschnitt der Ärztlichen Prüfung erfolgreich ab.
Nach Erhalt der Approbation begann ich meinen Dienst als Assistenzarzt der Inneren Abteilung am Elisabeth-Krankenhaus Essen.
Zum Juni 1981 erhielt ich meine Einberufung zum Grundwehrdienst, den ich als Geschwaderarzt des 5. Schnellbootgeschwaders in Kappeln/Olpenitz ableistete. Seit Sept. 1982 arbeite ich wieder als Assistenzarzt am Elisabeth-Krankenhaus Essen.
An meiner Dissertation habe ich bei Fr. Prof. Dr. Kupke zusammen mit Fr. B. Heller im Labor der Kinderklinik der Universität Düsseldorf seit dem Sommersemester 1977 gearbeitet.

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